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(54) **TRAITEMENT DU CANCER ET PREVENTION DES
METASTASES**

(54) **CANCER TREATMENT AND METASTASIS PREVENTION**

(57) A new method for the treatment of cancer in a human particularly malignant tumours, for example those in a breast or breasts, said method comprising the steps of: (1) directly injecting into the tumour a dosage amount of a pharmaceutical composition comprising an effective amount of an anti-cancer drug and/or drug suitable for use to treat cancer (for example about 1 to about 2 mg Novantrone [tm] (Mitoxantrone), other chemotherapeutic agent, NSAIDs) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water, and (2) administering systemically, preferably intravenously, a dosage amount of a pharmaceutical composition comprising (i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid/or pharmaceutically acceptable and salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce the side effects of any medicine (for example NSAID) administered therewith if the amount of the form of hyaluronic acid exceeds about 200 mg/70kg person) (ii) a drug selected from the group comprising (a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol); (b) an anti-cancer drug, and (c) a drug suitable for use to treat cancer and combinations thereof optionally together with (iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

ABSTRACT

A new method for the treatment of cancer in a human particularly malignant tumours, for example those in a breast or breasts, said method comprising the steps of:

(1) directly injecting into the tumour a dosage amount of a pharmaceutical composition comprising an effective amount of an anti-cancer drug and/or drug suitable for use to treat cancer (for example about 1 to about 2 mg Novantrone [tm] (Mitoxantrone), other chemotherapeutic agent, NSAIDs) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water, and

(2) administering systemically, preferably intravenously, a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid/or pharmaceutically acceptable and salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce the side effects of any medicine (for example NSAID) administered therewith if the amount of the form of hyaluronic acid exceeds about 200 mg/70kg person)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark

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Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol);

(b) an anti-cancer drug, and

(c) a drug suitable for use to treat cancer

and combinations thereof

optionally together with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

TITLE OF INVENTION

CANCER TREATMENT AND METASTASIS PREVENTION

FIELD OF INVENTION

This invention relates to the treatment of cancer and the prevention
5 of metastases in patients having cancer. This invention also relates to
pharmaceutical compositions and dosage amounts suitable for such treatment and
prevention. In one application this invention relates to the treatment of breast
cancer and the prevention of metastases in a patient with breast cancer.

BACKGROUND OF THE INVENTION

10 Conventional treatment of breast cancer involves a mastectomy, the
surgical removal of breast tissue. The procedure can vary from a simple
lumpectomy to the radical procedure during which the surgeon removes the
internal mammary chain of lymph nodes, the underlying pectoral muscles and
the adjacent axillary lymph nodes.

15 In the instances of early detection of cancers of the breast, breast
conserving therapy is now considered appropriate. Thus, lumpectomy together
with axillary clearance and radiotherapy are presently recommended as
alternatives. However, there is still considerable controversy surrounding the
ultimate minimum treatment to achieve adequate local control. This is true with
20 all cancers. In the considerations therefore, the choice of treatment will be made
to eliminate the cancer and ensure no recurrence, for example in the breast or
elsewhere by metastases.

Published application WO91/04058 provides a new treatment for
among other diseases, cancer providing for administration of dosage amounts of
25 pharmaceutical compositions comprising effective amounts of each of NSAIDs,
Vitamin C, anti-cancer agents, among other medicines and therapeutic agents
with a form of hyaluronic acid, for example sodium hyaluronate having a
molecular weight less than 750,000 daltons, in an amount equal to or exceeding 10
mg/70 kg person. At page 27, line 35 the document provides that the doses can be

administered intravenously, intra-arterially, intraperitoneally, intra-pleurally and directly into the tumour by injection through a needle placed under sonograph or CT guidance.

Case VII found at page 42-43 discloses the treatment of massive
5 cancer of the breast with supraclavicular and auxiliary lymph nodes palpable. The treatment involved combinations "of hyaluronic acid and/or salts thereof added to conventional chemotherapy used systemically by injection into the tumour and by intra-pleural cavity instillation" (page 45, lines 3-5).

The said document also teaches the systemic administration of
10 combinations of hyaluronic acid and/or salts thereof with NSAIDs (non-steroidal anti-inflammatory drug), ascorbic acid (Vitamin C), anti-cancer drugs among other drugs.

Publication WO/CA93/00061 relates to the topical treatment of skin diseases and conditions and involves the topical administration of specified dosage
15 amounts of pharmaceutical compositions taught. Basal cell carcinoma, for example is treated and resolved by such topical administration. The dosage amounts when discharged from the skin, unload into the lymphatic system (page 31, line 35). During their stay in the skin, particularly the epidermis, the drugs treat the disease or condition in the skin with the form of hyaluronic acid (for
20 example sodium hyaluronate having a molecular weight less than 750,000 daltons) transporting the drugs into the skin. Where an NSAID is used, synthesis of prostaglandin is inhibited, deblocking the macrophages and N.K. cells (page 26, line 27 to page 27, line 35) thereby permitting the macrophages and N.K. cells to destroy the disease or condition.

25 While the destruction/clearance of the malignant tumour and all cancer present is the end goal, it cannot be undertaken without concern for metastatic effects. Metastases and recurrence must be prevented particularly metastases into vulnerable organs such as the liver.

In the past treatments, not enough emphasis and concern was placed on the metastatic effect (metastases). Focus was on destruction and clearing. Thus, in the treatments prescribed or undertaken in the past, attempts were made to destroy the malignant tumour. However, prostaglandin synthesis in many approaches was permitted in the tissue (inhibiting the macrophages and N. K. cells from performing their function (killing cancer cells and destruction of the tumour)). Therefore cancer cells freed from the tumour instead of being destroyed, were permitted to travel in the body and lodge in a more vulnerable area (the liver or lungs, for example) - a certain recipe for metastases.

10 It is therefore an object of this invention to provide a new treatment for cancer which finds one particular application in the treatment of breast cancer.

It is a further object of this invention to reduce the risk of metastases with such treatment.

15 It is still a further object of the invention to reduce the risk of the recurrence of the disease, for example breast cancer.

It is still a further object of the invention to provide pharmaceutical compositions and dosage amounts of pharmaceutical compositions suitable for use in such treatments.

20 Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments.

SUMMARY OF THE INVENTION

Unexpectedly, Applicants have discovered a new treatment for cancer (for example breast cancer - malignant tumours of the breast) which not only causes the malignant tumours (such as those of the breast) to shrink, recede and disappear, but also unexpectedly reduces the risk of metastases.

According to one aspect of the invention, Applicants have provided a new method for the treatment cancer in a human particularly malignant

tumours, for example those in a breast or breasts, said method comprising the steps of:

5 (1) directly injecting into the tumour a non-toxic dosage amount of a pharmaceutical composition comprising an effective non-toxic amount of an anti-cancer drug and/or drug suitable for use to treat cancer (for example about 1 to about 2 mg Novantrone [tm] (Mitoxantrone) or other chemotherapeutic agent, (interferon or an NSAID) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water. (The size of the tumour will limit the amount that can be directly injected into the tumour.), and

15 (2) administering preferably systemically (preferably intravenously) a combination, preferably a dosage amount of a pharmaceutical composition, comprising

20 (i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce the side effects of any medicine (for

example NSAID) administered
therewith if the amount of the form
of hyaluronic acid exceeds about
200mg/70kg person)

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(ii) a drug selected from the group
comprising

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(a) a non-steroidal anti-inflammatory
drug (NSAID) for example in an effective
non-toxic amount of from about 30 mg to
about 100 mg (for example 30 to 60 mg of
tromethamine salt of ketoralac (sold under
the trade mark Toradol) and 50 to 100 mg
of diclofenac or diclofenac sodium (for
example sold under the trade mark
Voltarol);

15

(b) an effective nontoxic amount of a
chemotherapeutic agent as described in
(1) above (an anti-cancer drug, or drug
suitable to treat cancer, etc.)

20

and combinations thereof,
optionally with

(iii) an anti-oxidant for example
Vitamin C (in one embodiment 25
gm of Vitamin C).

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Where more than 200mg/70kg person of the form of hyaluronic acid
is used, adverse side effects of administering the drug (NSAID, chemotherapeutic
agent) are reduced if not eliminated.

The frequency of treatment for malignant tumours generally can be one (1) to four (4) times monthly or more (as may be required). For breast cancers, the frequency of the direct injections into the malignant tumour in the breast of pharmaceutical compositions of subparagraph (i) above and systemic 5 (intravenous) administration of a dosage amount of a pharmaceutical composition comprising

- 10 (i) an effective amount of a form of
hyaluronic acid (for example
hyaluronic acid and salts thereof
preferably sodium hyaluronate
having a molecular weight less
than 750,000 daltons (for example
15 150,000 - 225,000 daltons) for
example, about 100 - 200 mg of the
drug administered with the form of
hyaluronic acid with the amounts
of the form of hyaluronic acid
exceeding 200mg/70kg person or
more (because of a lack of toxicity)
- 20 (ii) a drug selected from the group
comprising a non-steroidal anti-
inflammatory drug (NSAID) for
example in an amount of from about
30 mg to about 100 mg (for example
25 30 to 60 mg of tromethamine salt of
ketoralac (sold under the trade
mark Toradol) and 50 to 100 mg of
diclofenac or diclofenac sodium (for
example sold under the trade mark

Voltarol); and

(b) an effective non-toxic amount of a
chemotherapeutic agent as described in (1)
above (an anti-cancer drug, or drug suitable to
treat cancer, etc.)

and combinations thereof,

optionally with

(iii) an anti-oxidant for example Vitamin C (in one
embodiment 25 gm of Vitamin C) is about one (1) to
three (3) times per month. (The form of hyaluronic
acid, for example sodium hyaluronate, transports
(causes the transport) of the medicines and therapeutic
agents into the tumour tissue for their destruction and
inhibits prostaglandin synthesis.)

Hyperthermia (heat) treatments may be applied to the breast having
the malignant tumour. Other regimens of therapeutic treatment may also be
given. For example as a precaution, depending on the amount of NSAID
administered and amount of sodium hyaluronate administered, an ulcerative
medicine such as Ranitidine may also be administered intravenously with sodium
hyaluronate.

In accordance with another aspect of the invention, Applicants have
provided a new method for the treatment of cancer, said method comprising the
steps of

(1) administering systemically (preferably intravenously)
to a human, a dosage amount comprising an effective non-toxic
amount of a drug suitable for treating cancer, alone or preferably
with an effective amount of a form of hyaluronic acid, for example,

hyaluronic acid or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) and

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(2) administering systemically (preferably intravenously) a dosage amount of a pharmaceutical composition comprising

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- (i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons

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(for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

- (ii) a drug selected from the group comprising

20

- (a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol);

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- (b) an effective non-toxic dosage amount of a chemotherapeutic agent for treating cancer

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and combinations thereof,

preferably with

(iii) an anti-oxidant for example

Vitamin C (in one embodiment

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25 gm of Vitamin C).

The steps are repeated over a period of time at chosen intervals suitable for the patient.

Unexpectedly and in accordance with another aspect of the invention, patients regularly administered dosage amounts described above over their period of
10 treatment, did not experience any metastatic effect (did not have any metastasis). Thus, their risk of metastases dramatically and surprisingly decreased substantially.

Thus, in accordance with another aspect of the invention, Applicants have provided a new treatment for the reduction of the risk of a
15 patient suffering from a cancer of having the cancer metastasize (reduce the risk of such patient suffering from a metastasis or suffering from a metastatic effect); said treatment comprising (preferably with other treatment for cancer for example those described above) administering systemically (preferably intravenously) a dosage amount of a pharmaceutical composition comprising

20

(i) an effective amount of a form of

hyaluronic acid (for example

hyaluronic acid and/or

pharmaceutically acceptable salts

thereof preferably sodium

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hyaluronate having a molecular

weight less than 750,000 daltons

(for example 150,000 - 225,000

daltons) for example about 100 - 200

mg or more (because of a lack of

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toxicity)

(ii) a drug selected from the group
comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)

5 for example in an effective non-toxic amount of
from for example about 30 mg to about 100 mg
(for example 30 to 60 mg of tromethamine salt of
ketoralac (sold under the trade mark Toradol)
and 50 to 100 mg of diclofenac or diclofenac
10 sodium (for example sold under the trade mark
Voltarol); and

(b) an effective non-toxic dosage amount of a

chemotherapeutic agent (an anti-cancer
agent or a drug suitable to treat cancer and
15 combinations thereof, preferably with

(iii) an anti-oxidant for example

Vitamin C (in one embodiment 25
gm of Vitamin C),
said administration continuing at
20 regular intervals (for example 1 - 4
times monthly) over the period the
treatment is being administered to
the patient for the treatment of the
cancer.

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Applicants believe that the above treatments are successful because
prostaglandin synthesis is inhibited thereby reactivating the macrophages and
N.K. cells to destroy the cancer, neoangiogenesis is prevented, or at least
precluded (by the combination of HA/NSAIDs), prostacyclin production is

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enhanced by the Vitamin C (sodium ascorbate) where used, and the hyaluronic acid (for example sodium hyaluronate) is cleared through the lymphatic system (by direct measurement the concentration of hyaluronan (occurring in the body) is 10 times higher in the lymph than the plasma. We have also observed a
5 prolonged effect after only a simple dose of medicine with HA (form of hyaluronic acid, for example sodium hyaluronate) which is, Applicants believe due to the fact that HA administered intravenously will track through the lymphatics. One would therefore anticipate an improved and prolonged effect in terms of immunosuppression for example with cyclosporin. This has been
10 confirmed in some initial experiments using intestinal allograft transplants in which the bowel is transplanted on an arterial venous pedicle but has all the lymphatics stripped off. Thus, when the drug enters through the arterial circulation it tracks into the lymphatics but there is no lymphatic drainage by which to exit from the bowel. The drug therefore remains in the grafts for a long
15 period. In our initial experiments one and two doses of cyclosporin in HA produced indefinite survival of the allograft).

Because the for example sodium hyaluronate transports, carries and causes the transport of the drug, the drug is also carried to and liberated in the lymph nodes. Because the blood stream will also take up for example the sodium
20 hyaluronate and thus the drug, the sodium hyaluronate and drug will be delivered to the liver (with the sodium hyaluronate transporting the drug into the tissue and cells of the liver). Thus, two major sites of nascent metastasis have for example sodium hyaluronate and drug (for example NSAID, anti-cancer drug) delivered to them with the sodium hyaluronate facilitating the transport of drug
25 into the tissue (of the lymph nodes and liver) wherein to prevent cancer development and/or metastasis. Thus, the sodium hyaluronate (and other forms of hyaluronic acid, including hyaluronic acid) can be administered systemically with a drug and such administration delivers the drug with the form of hyaluronic acid to the lymph nodes and liver. Such administration helps to

reduce the risk of metastasis and appears as a result of Applicant's tests to inhibit and even prevent metastasis of the cancer being treated in a human. Such administration may also be used to treat cancers in the lymph system and liver if cancer is found to be present there.

5 Where the cancer being treated is malignant tumours of the breast, and the treatment involves systemic administration, the direct injection (a number of times a month over the period of cancer treatment) of for example sodium hyaluronate with an anti-cancer drug and/or NSAID, the tumours reduced in size and cleared. Unexpectedly the reduction was without metastases.

10 Therefore, in accordance with another aspect of the invention, Applicants have provided new dosage amounts of pharmaceutical compositions in a form for systemic administration (usually intravenous administration from an IV bag), each such dosage amount comprising

- (i) an effective amount of a form of
- 15 hyaluronic acid (for example
- hyaluronic acid and
- pharmaceutically acceptable salts
- thereof preferably sodium
- hyaluronate having a molecular
- 20 weight less than 750,000 daltons
- (for example 150,000 - 225,000
- daltons) for example about 100 - 200
- mg or more (because of a lack of
- toxicity and to reduce side effects of
- 25 the medicine administered with the
- form of hyaluronic acid where the
- form of hyaluronic acid exceeds
- about 200mg/70kg person
- (ii) a drug selected from the group

comprising

- (a) a non-steroidal anti-inflammatory drug (NSAID)
for example in an effective non-toxic amount of
from about 30 mg to about 100 mg (for example 30
to 60 mg of tromethamine salt of ketoralac (sold
under the trade mark Toradol) and 50 to 100 mg
of diclofenac or diclofenac sodium (for example
sold under the trade mark Voltarol), and
- (b) an effective non-toxic dosage amount of a
chemotherapeutic agent (an anti-cancer
agent or a drug suitable to treat cancer and
combinations thereof, preferably with

(iii) an anti-oxidant for example

Vitamin C (in one embodiment 25
gm of Vitamin C).

In accordance with another aspect of the invention, Applicants have
provided new dosage amounts of a pharmaceutical composition for injection (in a
suitable form for injection) suitable for use with for example the above dosage
amount, said dosage amount being in the container or vial suitable for use for
injection (for example in a syringe) and comprising an effective amount of an
anti-cancer drug and/or a drug suitable for use to treat cancer (for example
breast cancer, in which event the dosage amount is injected into each tumour of
the breast) (for example about 1 to about 2 mg of Mitoxantrone) and an effective
amount of a form of hyaluronic acid, for example hyaluronic acid and/or
pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having
a molecular weight less than 750,000 daltons (for example 150,000 - 225,000
daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile
water.

Therefore Applicants have provided the use of a new dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of
hyaluronic acid (for example
hyaluronic acid and/or
pharmaceutically acceptable salts
thereof preferably sodium
hyaluronate having a molecular
weight less than 750,000 daltons
(for example 150,000 - 225,000
daltons) for example about 100 - 200
mg or more (because of a lack of
toxicity).

(ii) an effective non-toxic amount of a
drug selected from the group
comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)
for example in an amount of from about 30 mg to
about 100 mg (for example 30 to 60 mg of
tromethamine salt of ketoralac (sold under the
trade mark Toradol) and 50 to 100 mg of
diclofenac or diclofenac sodium (for example sold
under the trade mark Voltarol); and an effective
non-toxic amount of a chemotherapeutic agent
(anti-cancer agent or an agent suitable to treat
cancer)

and combinations thereof and preferably with

(iii) an anti-oxidant for example
Vitamin C (in one embodiment 25

gm of Vitamin C) for

- (a) the treatment of cancer in a patient, and (b) the prevention of metastasis in a patient suffering from cancer.

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Furthermore Applicants have provided the use of

(A) a dosage amount of a pharmaceutical composition for injection (in a suitable form for injection), said dosage amount being in the container or vial for injection and comprising an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer (for example breast cancer, in which event the dosage amount is to be injected into each tumour of the breast) (for example about 1 to about 2 mg of Mitoxantrone and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water; and

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(B) a dosage amount comprising

- (i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

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(ii) an effective non-toxic amount of a
drug selected from the group
comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)
for example in an amount of from about 30 mg to
about 100 mg (for example 30 to 60 mg of
tromethamine salt of ketoralac (sold under the
trade mark Toradol) and 50 to 100 mg of
diclofenac or diclofenac sodium (for example sold
under the trade mark Voltarol) and

(b) an effective non-toxic amount of a
chemotherapeutic agent (anti-cancer agent or
an agent suitable to treat cancer);

and combinations thereof; preferably with;

(iii) an anti-oxidant for example

Vitamin C (in one embodiment 25
gm of Vitamin C).

(a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from
cancer and/or

(c) delivery of the drug to the lymph system and/or liver.

Applicants have further provided the use of each of
(I) non-toxic dosage amounts of a pharmaceutical composition
for injection (in a suitable form for injection), said dosage
amount being in the container or vial for injection and
comprising an effective amount of an anti-cancer drug
and/or a drug suitable for use to treat cancer (for example
breast cancer, in which event the dosage amount is injected
into each tumour of the breast) (for example about 1 to about 2

mg of Mitoxantrone and an effective amount of a form of
hyaluronic acid, for example hyaluronic acid and/or
pharmaceutically acceptable salts thereof, preferably sodium
hyaluronate having a molecular weight less than 750,000
5 daltons (for example 150,000 - 225,000 daltons) (for example
about 10 to about 20 mg sodium hyaluronate) in sterile water
and

(II) a non-toxic dosage amount comprising

(i) an effective amount of a form of
10 hyaluronic acid (for example
hyaluronic acid and/or
pharmaceutically acceptable salts
thereof preferably sodium
hyaluronate having a molecular
weight less than 750,000 daltons
(for example 150,000 - 225,000
daltons) for example; about 100 - 200
mg or more (because of a lack of
toxicity)

20 (ii) a drug selected from the group
comprising

- (a) a non-steroidal anti-inflammatory drug (NSAID)
for example in an amount of from about 30 mg to
about 100 mg (for example 30 to 60 mg of
25 tromethamine salt of ketoralac (sold under the
trade mark Toradol) and 50 to 100 mg of
diclofenac or diclofenac sodium (for example sold
under the trade mark Voltarol) and
(b) a therapeutically effective non-toxic dosage

amount of a chemotherapeutic agent (anti-cancer agent or an agent to treat cancer) and combinations thereof, optionally with preferably

(iii) an anti-oxidant for example

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Vitamin C (in one embodiment 25 gm of Vitamin C)

for (a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient

suffering from cancer and/or

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(c) delivery of a drug to the lymph system and/or liver.

Applicants have also provided each of

(A) an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to

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treat cancer (for example breast cancer, in

which event the dosage amount is injected into

each tumour of the breast) (for example about 1

to about 2 mg of Mitoxantrone and an effective

amount of a form of hyaluronic acid, for example

hyaluronic acid and/or pharmaceutically

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acceptable salts thereof, preferably sodium

hyaluronate having a molecular weight less

than 750,000 daltons (for example 150,000 -

225,000 daltons) (for example about 10 to about 20

mg sodium hyaluronate) in sterile water and

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(B)

(i) an effective amount of a form of hyaluronic acid (for example

hyaluronic acid and/or

pharmaceutically acceptable salts

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thereof preferably sodium
hyaluronate having a molecular
weight less than 750,000 daltons
(for example 150,000 - 225,000
daltons) for example about 100 - 200
mg or more (because of a lack of
toxicity)

(ii) a drug selected from the group
comprising

- (a) a non-steroidal anti-inflammatory drug
(NSAID) for example in an amount of from
about 30 mg to about 100 mg (for example
30 to 60 mg of tromethamine salt of
ketoralac (sold under the trade mark
Toradol) and 50 to 100 mg of diclofenac or
diclofenac sodium (for example sold under
the trade mark Voltarol); and
- (b) an effective non-toxic dosage amount of a
chemotherapeutic agent (for example an
anti-cancer agent or an agent to treat
cancer)

and combinations thereof; with preferably

(iii) an anti-oxidant for example
Vitamin C (in one embodiment 25
gm of Vitamin C).

for the manufacture of two
pharmaceutical compositions, one
from the components of (A) and one
from the components of (B), each

A

for the treatment of cancer,
prevention of metastases and/or
delivery of a drug to the lymph
system and/or liver.

Suitable forms of sodium
hyaluronate may include a fraction
supplied by Hyal Pharmaceutical
Corporation supplied in a 15 ml vial
of sodium hyaluronate 20mg/ml
(300mg/vial - Lot 2F3). The sodium
hyaluronate fraction is a 2%
solution with a mean average
molecular weight of about 225,000

daltons. The fraction also contains
water q.s. which is triple distilled
and sterile in accordance with the
U.S.P. for injection formulations.

The vials of hyaluronic acid and/or
salts thereof may be carried in a
Type 1 borosilicate glass vial closed
by a butyl stopper which does not
react with the contents of the vial.

The fraction of hyaluronic acid
and/or salts thereof (for example
sodium salt) and homologues,
analogues, derivatives, complexes,
esters, fragments, and sub-units of
hyaluronic acid, preferably
hyaluronic acid and salts thereof,

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may comprise hyaluronic acid
and/or salts thereof having the
following characteristics:

a purified, substantially pyrogen-
free fraction of hyaluronic acid
obtained from a natural source
having at least one characteristic
selected from the group (and
preferably all characteristics)
consisting of the following:

- i) a molecular weight within the
range of 150,000-225,000 daltons;
- ii) less than about 1.25% sulphated
mucopoly-saccharides on a total
weight basis;
- iii) less than about 0.6% protein on a
total weight basis;
- iv) less than about 150 ppm iron on a
total weight basis;
- v) less than about 15 ppm lead on a
total weight basis;
- vi) less than 0.0025% glucosamine;
- vii) less than 0.025% glucuronic acid;
- viii) less than 0.025% N-
acetylglucosamine;
- ix) less than 0.0025% amino acids;
- x) a UV extinction coefficient at 257
nm of less than about 0.275;
- xi) a UV extinction coefficient at 280

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- nm of less than about 0.25; and
- xii) a pH within the range of 7.3-7.9.
- Preferably, the hyaluronic acid is mixed with water and the fraction of hyaluronic acid has a mean average molecular weight within the range of 150,000-225,000. More preferably, the fraction of hyaluronic acid may comprise at least one characteristic selected from the group (and preferably all characteristics) consisting of the following characteristics:
- i) less than about 1% sulphated mucopolysaccharides on a total weight basis;
 - ii) less than about 0.4% protein on a total weight basis;
 - iii) less than about 100 ppm iron on a total weight basis;
 - iv) less than about 10 ppm lead on a total weight basis;
 - v) less than 0.00166% glucosamine;
 - vi) less than 0.0166% glucuronic acid;
 - vii) less than 0.0166% N-acetylglucosamine;
 - viii) less than 0.00166% amino acids;
 - x) a UV extinction coefficient at 257 nm of less than about 0.23;

- xi) a UV extinction coefficient at 280 nm of less than 0.19; and
- xii) a pH within the range of 7.5-7.7

Applicants also propose to use sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc., having the following specifications:

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	<u>Characteristics</u>	<u>Specification</u>
	Appearance	White to cream colored particles
	Odor	No perceptible odor
5	Viscosity Average	< 750,000 Daltons
	Molecular Weight	
	UV/Vis Scan, 190-820nm	Matches reference scan
	OD, 260nm	< 0.25 OD units
	Hyaluronidase Sensitivity	Positive response
10	IR Scan	Matches reference
	pH, 10mg/g solution	6.2 - 7.8
	Water	8% maximum
	Protein	< 0.3 mcg/mg NaHy
	Acetate	< 10.0 mcg/mg NaHy
15	Heavy Metals, maximum ppm	
	As Cd Cr Co Cu Fe Pb Hg Ni	
	2.0 5.0 5.0 10.0 10.0 25.0 10.0 10.0 5.0	
	Microbial Bioburden	None observed
	Endotoxin	< 0.07EU/mg NaHy
20	Biological Safety Testing	Passes Rabbit Ocular Toxicity Test

Another form of sodium hyaluronate is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

25 Specifications' Test

Results

Lot No.	HG1004
pH	6.12
Chondroitin Sulfate	not detected

A

	Protein	0.05%
	Heavy Metals	Not more than 20 ppm
	Arsenic	Not more than 2 ppm
	Loss on Drying	2.07%
5	Residue on Ignition	16.69%
	Intrinsic Viscosity	12.75 dl/s (XW: 679,000)
	Nitrogen	3.14%
	Assay	104.1%
	Microbiological Counts	80/g
10	E. coli	Negative
	Mold and Yeast	Not more than 50/g

Other forms of hyaluronic acid and/or its salts, and analogues, homologues, derivatives, complexes, esters, fragments and sub units of hyaluronic acid may be chosen from other suppliers, for example those described in prior art documents provided the form of hyaluronic acid chosen is suitable for transport of the medicine.

The following references teach hyaluronic acid, sources thereof, and processes for the manufacture and recovery thereof which may prove to be suitable.

United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

- "(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 cm³/g., and preferably greater than about 2000 cm³/g.;
- (b) a protein content of less than 0.5% by weight;
- (c) ultraviolet light absorbance of a 1% solution of sodium hyaluronate of less than 3.0 at 257

nanometers wavelength and less than 2.0 at 280

nanometers wavelength;

(d) a kinematic viscosity of a 1% solution of sodium
hyaluronate in physiological buffer greater than
5 about 1000 centistokes, preferably greater than
10,000 centistokes;

(e) a molar optical rotation of a 0.1 - 0.2% sodium
hyaluronate solution in physiological buffer of
less than -11×10^3 degree $\cdot \text{cm}^2/\text{mole}$ (of
10 disaccharide) measured at 220 nanometers;

(f) no significant cellular infiltration of the vitreous
and anterior chamber, no flare in the aqueous
humour, no haze or flare in the vitreous, and no
pathological changes to the cornea, lens, iris,
15 retina, and choroid of the owl monkey eye when
one milliliter of a 1% solution of sodium
hyaluronate dissolved in physiological buffer is
implanted in the vitreous replacing approximately
one-half the existing liquid vitreous, said HUA
20 being

(g) sterile and pyrogen free and

(h) non-antigenic."

Canadian Letters Patent 1,205,031 (which refers to United States
Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average
25 molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to
730,000 and discusses processes of their manufacture.

The invention will now be illustrated with reference to the
following data relating to persons suffering from cancer. A schedule of the
dosage amounts received by each patient is attached and refers to the letter used

to identify the patient. The chronology of the administration of the dosage amounts in each Schedule is in reverse order with the dosage given earliest being at the end of the Schedule and the most recent dosage being at the beginning of the Schedule.

PATIENTS TREATED

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EXAMPLE 1

Patient A - aged 42 (Female)

- breast cancer occupying the entire breast, no previous treatment
- 5 - treated with NSAIDs, sodium ascorbate, HA intravenously plus systemic therapy
- also injected with Novantrone/HA on 4 occasions
- complete response with total regression of local tumour, has not developed any metastases
- see Schedule A for dosages (HA = sodium hyaluronate having molecular weight
- 10 less than 750,000 daltons)

EXAMPLE 2

Patient B - aged 60 (Female)

- local recurrence after a regional excision
- treated by direct injection with Novantrone/HA 1 mg plus 10 mgs of HA at 4
- 15 different times
- also received NSAIDs/HA intravenously
- her tumour has regressed 75% of its original size over 1.5 years
- has not developed any metastases
- see Schedule B for dosages

20 EXAMPLE 3

Patient C (Female)

- received the dosages in Schedule C including direct injection into tumours (IT)
- in breast, including direct injection and intravenous administration (IV)
- surprisingly the tumours disappeared with no metastasis

25 EXAMPLE 4

Patient D (Female)

- received dosage amounts in Schedule D including direct injection(IT) into the
- tumours in the breast and intravenous (IV) administration
- patient held her own

EXAMPLE 5

Patient E - aged 55 (Female)

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- carcinoma of the breast, treated with NSAIDs/HA and sodium ascorbate intravenously only (direct injections as well)
- 5 - has not metastasized from the position of tumour in the supraclavicular nodes over the past three years
- see Schedule E for dosages

EXAMPLE 6

Patient F - aged 73 (Female)

- 10 - carcinoma of the breast with liver metastases treated over 3 years with NSAIDs, HA, sodium ascorbate plus chemotherapy intravenously (IV);
- tumour was stable then began to grow but no metastases developed in this entire time (no injections appear to have been given into breast; however injections made into neck node left side)
- 15 - she discontinued treatment because of her age
- see Schedule F for dosages

EXAMPLE 7

Patient G - aged 56 (Female)

- carcinoma of the breast metastatic to supraclavicular nodes, disease has been
- 20 stable for 4 years as a result of intermittent treatment with NSAIDs, sodium ascorbate and HA intravenously
- no direct injection
- see Schedule G for dosage amounts

EXAMPLE 8

25 Patient H - aged 81 (Female)

- carcinoma of the right lung with metastases to the mediastinum at diagnosis
- treated with weekly NSAIDs, sodium ascorbate, HA intravenously
- tumour remained stable without metastases and terminally some local growth
- treatment was discontinued as she was 81 years old, disabled and did not wish

further therapy

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- she died of cardiac failure
- see Schedule H for dosage amounts

EXAMPLE 9

5 Patient I - aged 64 (Male)

- carcinoma of the prostate, remains entirely stable on NSAIDs/HA and sodium ascorbate given intravenously
- Schedule I sets out dosages

EXAMPLE 10

10 Patient J - aged 65 (Male)

- carcinoma of the colorectum metastatic to the liver, stable for 2 years without metastases
 - treated one to two times per week with sodium ascorbate/HA and NSAIDs intravenously
- 15 - see Schedule J for dosage amounts

The following additional experimental data illustrates our results in the treatment of breast cancer patients. We have used by systemic administration, NSAIDs, sodium ascorbate and HA experimentally in these patients over a number of years. We have treated experimentally a total of 63 patients who had minimal surgery wherever possible. Patients received hormone blocking agents if they were positive for oestrogen or progesterone receptors. Only occasionally was an oophorectomy performed. We utilized low doses of chemotherapy, employing methotrexate (100 mg/100 mg HA on the first day) and 5-fluorouracil (5-FU) (350-500 mg/100 mg HA on the second and third days), initially without HA and subsequently with HA by injection. Where the tumour was considered more aggressive we used a four-drug combination in the injections (see Table 1).

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TABLE 1

Treatment for cancer of the breast

1. Surgery		
	Modified radical mastectomy	23 patients
5	Segmental resection and lymph node dissection	40 patients
2. Hormone manipulation		
	Tamoxifen given	33/63 patients
	Surgical oophorectomy	3/63 patients
3. Chemotherapy		
10	Combination of MTX(mitoxantrone)+5-FU(5-FLUOROURACIL)	
	or	
	Combination of novantrone, 5-FU, mitomycin C, MTX (MITOXANTRONE)	
4. Radiation		
15	One case	
5. Hyperthermia		
	EMW 915 MHz	Since 1982,
	to area of cancer	all patients
6. Immune modulation		
20	(a) Non-specific immune enhancement	
	(b) Modification with PGE2 inhibitors high dose sodium ascorbate	
	Radiation was avoided. In these patients hyperthermia was employed by microwave technique to enhance the effect of the drugs. We have thus achieved a 90% survival for as long as nine years (see Table 2).	

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TABLE 2

Cancer of the breast. Patients and survival

	No. of patients:	63
	Stage of disease:	I-14
5		II-49
	Age: Range	27-75
	Mean	43 years
	No. surviving free of cancer	55
	Average survival time in years	8
10	No. surviving with disease	6
	No. died of disease	2

It is apparent from these results that moderate doses of chemotherapy, adding NSAIDs and giving the drugs in HA, has resulted in an improved survival rate in a group of patients at high risk for recurrent disease.

15 An alternative experimental treatment for local breast cancer with or without systemic diseases was also devised. In one group of patients the initial four patients refused surgery and/or radiation. One had a recurrence in both breasts post-radiation; another post-radiation patient had skeletal metastases at the time of presentation. We injected mitoxantrone 1 mg in 10 mg HA from 1 to 6
20 times until the tumour disappeared. In addition, we gave systemic chemotherapy in HA and hyperthermia. Where appropriate, hormone-blocking drugs were used. Altogether 10 patients were treated in this fashion. All had a complete response in terms of regression of local disease (see Table 3).

TABLE 3

Alternative experimental treatment of breast cancer
Patients

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1. 10 patients treated experimentally over years
- 5 4 recurrent after surgery
- 1 recurrent post-irradiation
- both breasts affected
2. 1/10 had distant metastases when diagnosed
- All had positive axillary lymph nodes

10 Results

- 10/10 complete local and regional node response
- 2/10 (initial patients) died of systemic disease
- 8/10 alive and well. Mean survival time=3 years
- Cosmetic result is excellent

15

The local reaction was not excessive although it consisted on initial enlargement of the area of the tumour site. What was impressive was the return of the breast to normal in some instances, and with only minimal scar tissue apparent on mammography in others.

20

This is a unique method of treatment. It appears that the drugs administered in HA affect almost exclusively the tumour tissue and do not produce a significant effect on normal tissue.

25

As many changes can be made to the dosage amounts used in the examples without departing from the scope of the inventions, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. The use of:

(1) (a) an effective non-toxic dosage amount of an anti-cancer drug and/or drug suitable for use to treat cancer; and

(b) an effective dosage amount of a form of hyaluronic acid; in the manufacture of a first pharmaceutical composition for direct injection into a tumour wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water, and

(2) (a) an effective amount of a form of hyaluronic acid;

(b) a drug selected from the group comprising:

(i) a non-steroidal anti-inflammatory drug (NSAID);

(ii) a chemotherapeutic agent;

and combinations thereof optionally with

(c) an anti-oxidant

in the manufacture of a second pharmaceutical composition for systemic administration wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons and wherein both the first and second compositions are useful for the treatment of cancer in a human for the prevention of metastases in the human.

2. The use of claim 1 wherein the form of hyaluronic acid is sodium hyaluronate.

3. The use of claim 1 or 2 wherein the form of cancer to be treated is breast

B

cancer.

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4. The use of claim 1, 2 or 3 wherein the systemic administration is intravenous administration.

5. The use of claim 1, 2, 3 or 4 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

6. The use of claim 1, 2, 3, 4 or 5 wherein the chemotherapeutic agent is novantrone.

7. The use of claim 1, 2, 3, 4, 5 or 6 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

8. The use of claim 1, 2, 3, 4, 5, 6 or 7 wherein the anti-oxidant is Vitamin C.

9. The use of:

(1) (a) an effective non-toxic dosage amount of an anti-cancer drug and/or drug suitable for use to treat cancer; and

(b) an effective dosage amount of a form of hyaluronic acid; in the manufacture of a first pharmaceutical composition for direct injection into a tumour wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water, and

(2) (a) an effective amount of a form of hyaluronic acid;

(b) a drug selected from the group comprising:

(i) a non-steroidal anti-inflammatory drug (NSAID);

(ii) a chemotherapeutic agent;

B

and combinations thereof optionally with

(c) an anti-oxidant

in the manufacture of a second pharmaceutical composition for systemic administration wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons and wherein both the first and second compositions are useful for the treatment of cancer in a human for the reduction of metastases in the human.

10. The use of claim 9 wherein the form of hyaluronic acid is sodium hyaluronate.

11. The use of claim 9 or 10 wherein the form of cancer to be treated is breast cancer.

12. The use of claim 9, 10 or 11 wherein the systemic administration is intravenous administration.

13. The use of claim 9, 10, 11 or 12 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

14. The use of claim 9, 10, 11, 12 or 13 wherein the chemotherapeutic agent is novantrone.

15. The use of claim 9, 10, 11, 12, 13 or 14 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

16. The use of claim 9, 10, 11, 12, 13, 14 or 15 wherein the anti-oxidant is Vitamin C.

17. The use of:

(1) (a) an effective non-toxic dosage amount of an anti-cancer drug and/or drug suitable for use to treat cancer; and

(b) an effective dosage amount of a form of hyaluronic acid; in the manufacture of a first pharmaceutical composition for direct injection into a tumour wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water, and

(2) (a) an effective amount of a form of hyaluronic acid;

(b) a drug selected from the group comprising:

(i) a non-steroidal anti-inflammatory drug (NSAID);

(ii) a chemotherapeutic agent;

and combinations thereof optionally with

(c) an anti-oxidant

in the manufacture of a second pharmaceutical composition for systemic administration wherein the form of hyaluronic acid is selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons and wherein both the first and second compositions are useful for the treatment of cancer in a human for the reduction of the risk of a patient suffering from a cancer having the cancer metastasize (reduce the risk of such patient suffering from a metastasis or suffering from a metastatic effect) of metastases in the human.

18. The use of claim 17 wherein the form of hyaluronic acid is sodium hyaluronate.

19. The use of claim 17 or 18 wherein the form of cancer to be treated is breast cancer.

20. The use of claim 17, 18 or 19 wherein the systemic administration is intravenous administration.

21. The use of claim 17, 18, 19 or 20 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

22. The use of claim 17, 18, 19, 20 or 21 wherein the chemotherapeutic agent is novantrone.

23. The use of claim 17, 18, 19, 20, 21 or 22 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

24. The use of claim 17, 18, 19, 20, 21, 22 or 23 wherein the anti-oxidant is Vitamin C.

25. A combination of dosage amounts of pharmaceutical compositions comprising (1) a non-toxic dosage amount of a first pharmaceutical composition in a form for systemic administration comprising

- (i) an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons; and
- (ii) a drug selected from the group comprising
 - (a) a non-steroidal anti-inflammatory drug (NSAID); and
 - (b) a chemotherapeutic agentand combinations thereof and optionally;

(iii) an anti-oxidant; and

(2) a non-toxic effective dosage amount of a second pharmaceutical composition in an injectable form comprising (i) an effective non-toxic amount of an anti-cancer drug and/or a drug suitable for use to treat cancer, and (ii) an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons in sterile water.

26. The combination of claim 25 wherein the form of hyaluronic acid is sodium hyaluronate.

27. The combination of claim 25 or 26 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

28. The combination of claim 25, 26 or 27 wherein the chemotherapeutic agent is novantrone.

29. The combination of claim 25, 26, 27 or 28 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

30. The combination of claim 25, 26, 27, 28 or 29 wherein the anti-oxidant is Vitamin C.

31. The use of effective non-toxic dosage amounts of pharmaceutical compositions, one said dosage amount comprising an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective dosage amount of a form of hyaluronic acid, selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in

sterile water, suitable for injection and another dosage amount comprising

- (i) an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons, and
- (ii) a drug selected from
 - (a) a non-steroidal anti-inflammatory drug (NSAID), and
 - (b) a chemotherapeutic agentand combinations thereof optionally with
- (iii) an anti-oxidant

for (a) the treatment of cancer in a patient, (b) the prevention of metastasis in a patient suffering from cancer, and (c) the delivery of a drug to the lymph system and/or liver.

32. The use of claim 31 wherein the form of hyaluronic acid is sodium hyaluronate.

33. The use of claim 31 or 32 wherein the form of cancer to be treated is breast cancer.

34. The use of claim 31, 32 or 33 wherein the systemic administration is intravenous administration.

35. The use of claim 31, 32, 33 or 34 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

36. The use of claim 31, 32, 33, 34 or 35 wherein the chemotherapeutic agent is novantrone.

37. The use of claim 31, 32, 33, 34, 35 or 36 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

38. The use of claim 31, 32, 33, 34, 35, 36 or 37 wherein the anti-oxidant is Vitamin C.

39. The use of each of

(I) a dosage amount of a pharmaceutical composition for systemic administration comprising an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer alone in a suitable excipient or optionally with an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons; and

(II) an effective dosage amount comprising

(i) an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons, and

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)

(b) a chemotherapeutic agent

and combinations thereof

and optionally

(iii) an anti-oxidant for

(a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from cancer, and

(c) the delivery of a drug to the lymph system and/or liver.

40. The use of claim 39 wherein the form of hyaluronic acid is sodium hyaluronate.

41. The use of claim 39 or 40 wherein the form of cancer to be treated is breast cancer.

42. The use of claim 39, 40 or 41 wherein the systemic administration is intravenous administration.

43. The use of claim 39, 40, 41 or 42 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

44. The use of claim 39, 40, 41, 42 or 43 wherein the chemotherapeutic agent is novantrone.

45. The use of claim 39, 40, 41, 42, 43 or 44 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

46. The use of claim 39, 40, 41, 42, 43, 44 or 45 wherein the anti-oxidant is Vitamin C.

47. The use of an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water in the manufacture of a pharmaceutical composition for the prevention of metastases in a patient

suffering from cancer.

48. The use of claim 47 wherein the form of hyaluronic acid is sodium hyaluronate.

49. The use of claim 47 or 48 wherein the form of cancer to be treated is breast cancer.

50. The use of claim 47, 48 or 49 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

51. The use of claim 47, 48, 49 or 50 wherein the pharmaceutical composition is in injectible form.

52. The use of

- (i) an effective dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons, and
- (ii) a drug selected from
 - (a) a non-steroidal anti-inflammatory drug (NSAID)
 - (b) a chemotherapeutic agentand combinations thereof optionally with
- (iii) an anti-oxidant in the manufacture of a pharmaceutical composition for the prevention of metastases in a patient suffering from cancer.

53. The use of claim 52 wherein the form of hyaluronic acid is sodium hyaluronate.

54. The use of claim 52 or 53 wherein the form of cancer to be treated is breast cancer.

55. The use of claim 52, 53 or 54 wherein the pharmaceutical composition is in a form for intravenous administration.

56. The use of claim 52, 53, 54 or 55 wherein the chemotherapeutic agent is novantrone.

57. The use of claim 52, 53, 54, 55 or 56 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

58. The use of claim 52, 53, 54, 55, 56 or 57 wherein the anti-oxidant is Vitamin C.

59. The use of

- (I) an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water; and
- (II) (i) an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons, and
- (ii) a drug selected from
 - (a) a non-steroidal anti-inflammatory drug (NSAID); and

- (b) a chemotherapeutic agent
and combinations thereof optionally with
- (iii) an anti-oxidant in the manufacture of two pharmaceutical compositions, composition (1) comprising the components of (I) and composition (2) comprising the components of (II) for
 - (a) the treatment of cancer in a patient,
 - (b) the prevention of metastasis in a patient suffering from cancer, and
 - (c) the delivery of a drug to the lymph system and/or liver.

60. The use of claim 59 wherein the form of hyaluronic acid is sodium hyaluronate.

61. The use of claim 59 or 60 wherein the form of cancer to be treated is breast cancer.

62. The use of claim 59, 60 or 61 wherein the systemic administration is intravenous administration.

63. The use of claim 59, 60, 61 or 62 wherein the anti-cancer drug and/or drug suitable for use to treat cancer is novantrone.

64. The use of claim 59, 60, 61, 62 or 63 wherein the chemotherapeutic agent is novantrone.

65. The use of claim 59, 60, 61, 62, 63 or 64 wherein the non-steroidal anti-inflammatory drug is diclofenac sodium.

66. The use of claim 59, 60, 61, 62, 63, 64 or 65 wherein the anti-oxidant is Vitamin C.

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